Remarks

In response to the final rejection of December 30, 2005, Applicants submitted a Notice of Appeal on February 14, 2006. By virtue of the filing of a Request for Continued Examination submitted herewith, the present amendment is now entered into the application.

Claims 1-4, 7, 8 and 13-16 are pending in the application. Claims 1, 3, 7, 8, 13 and 15 have been rejected. Claims 2, 4, 14 and 16 have been objected to and have been indicated as allowable. Claims 1, 2, 4, 7, 8, 13, 14 and 16 have been amended. It is noted that in claims 2 and 14, the second and fifth compounds inadvertently contained an extra carbon atom yielding a single linear chain of 6 carbon atoms. Claims 2 and 14 have been amended to show that compounds 2 and 5 have a single linear chain of 5 carbons atoms instead of 6 carbon atoms. Support for this amendment can be found in the specification on page 14a, Table (B), compound nos. 5 and 8 (corresponding to compounds 2 and 5 in amended claims 2 and 14). Claims 3 and 15 have been cancelled without prejudice. No new matter has been added.

Claims 1, 3, 7, 8, 13 and 15 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Lobaccaro et al., J. Med. Chem. Vol 40, pp. 2217-2227, 1997 (Lobaccaro et al.). The Examiner essentially contends that since 1) the presently claimed compounds are homologs of the 11β-n-alkyl estradiol derivatives described in Lobaccaro et al.; 2) Lobaccaro et al. teach that the substituent at the 11β-position increases and improves the binding affinity for the estrogen receptor; 3) the length of the 11β-n-alkyl arm affects the binding affinity for the estrogen receptor; and 4) the compounds in Lobacarro et al. show ER-β antagonist and ER-α agonist activity (examiner's citation to Lobaccaro on page 2219, the right column to page 2221, Table 2), it would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the presently claimed 11β-n-alkyl estradiols in a method for treating estrogen deficiency disorders and a method of inducing ER-α agonist activity and ER-β antagonist activity in a patient in need thereof. The Examiner also indicates that the unexpected results of the claimed invention over the prior art are found persuasive as to claims 2, 4, 14 and 16.

As independent claims 1, 8 and 13 have been amended, Applicants address the above rejection with respect to the amended claims. Applicants traverse the rejection and respectfully submit that Lobaccaro et al. does not make obvious amended independent claims 1, 8 and 13.

At the outset, the arguments previously presented in the response of August 23, 2005 are incorporated by reference herein.

Lobaccaro et al. is directed to the development of steroidal affinity labels of the estrogen receptor, in particular, two estradiol 11β-ethyl derivatives, three estradiol 11β-butyl derivatives,

and one estradiol 11β-decyl derivative. Lobaccaro does not teach or specifically suggest the 11 β-n-alkyl estradiols having a length of 5 to 6 carbon atoms. While Lobaccaro et al. teach that the length of the 11β-n-alkyl arm affects the binding affinity for the estrogen receptor the Examiner, in stating that "these compounds show ER-β antagonist and ER-α agonist activity." mischaracterizes and simplifies the teachings of Lobaccaro et al. In this regard, the Examiner's attention is directed to page 2221, column 1 which refers to Table 2. Therein, it states:

> "Activity of the electrophilic compounds (Figure 3, Table 2) was not correlated with the whole 11 β-substituent, but rather with the alkyl part of the substitutent, since the two estradiol 11β-ethyl derivatives 12a and 13a mainly displayed estrogenic activity, wherein the three estradiol 11 β-butyl derivatives 12b, 13b, and 14 and the 11β-decyl derivative 20 showed almost pure antiestrogenic activity."

The Examiner's attention is also directed to page 2223, column 1, second paragraph, which states:

> "The estradiol electrophilic 11β-derivatives proved to be either [emphasis added] estrogenic (11β-ethyl compounds) or antiestrogenic (11β-butyl and 11β-decyl compounds)."

Accordingly, Lobaccaro et al. does not simply teach that the described 11β-n-alkyl estradiol derivatives have both agonist and antagonist activity, but instead that the 11β-n-alkyl estradiol derivatives with an alkyl arm of 2 carbon atoms possess agonist activity whereas the 11β-n-alkyl estradiol derivatives with an alkyl arm of 4 or 10 carbon atoms possess antagonist activity. There is absolutely no teaching or specific suggestion that an 11β-n-alkyl estradiol derivative having an alkyl arm of 5 to 6 carbon atoms would possess selective affinity for both ER-α and ER-β receptors. Indeed, it may be fairly stated that one skilled in the art, reviewing Table 2 and seeing that 11β-n-alkyl estradiol derivatives with an alkyl arm of two carbon atoms possess agonist activity and that 11β-n-alkyl estradiol derivatives with an alkyl arm of 4 or 10 carbon atoms possess antagonist activity, would reasonably expect that alkyl lengths in between the length of 4 and 10 carbons would also possess antagonist activity. This reasonable expectation is further supported by the statement in Lobaccaro et al. on page 2223, left column, second paragraph, wherein it states:

> "....with estradiol 11β-substituted derivatives, it appears that the threshold which separates estrogenic from antiestrogenic compounds is rapidly reached when the size of the 11β-alkyl chain increases, with a threshold between C-2 and C-4. "

Accordingly, since 1) there is no teaching or specific suggestion in Lobaccaro et al. of 11β-n-alkyl estradiol derivatives having an alkyl arm of 5 to 6 carbon atoms, or that such derivatives can be used to treat estrogen deficiency disorders by inducing ERα agonist activity and ERβ-antagonist activity, and 2) one skilled in the art viewing Lobaccaro et al. would not reasonably expect that 11β-n-alkyl estradiol derivatives having an alkyl arm of 5 to 6 carbon

atoms would possess selective affinity for both ER-α and ER-β receptors, Lobaccaro et al. does not establish a *prima facie* case of obviousness.

An analysis of obviousness of a claimed compound must also include consideration of the results achieved by the claimed compound. Applicants have previously presented a 37 C.F.R. §1.132 Declaration where pharmacologist Antwan Ederveen declared that the differential properties observed between the C4 (an agonist on ERα, see specification, Compound 4 of Table 2) and C5 (an agonist on ERα and antagonist on ERβ) 11β-derivatives is unexpected and does not follow in any way from the teachings of Lobaccaro et al. As amended claims 1, 8 and 13 recite 11β estradiol derivatives having an R_{11} linear chain of 5 to 6 carbon atoms, it is respectfully submitted that the unexpected results are commensurate in scope with the amended claims.

In sum, in view that a *prima facie* case of obviousness has not been established and taking into consideration the unexpected results achieved by the claimed compound, Lobaccaro et al. does not make obvious claims 1, 3, 7, 8, 13 and 15.

In view of the above, withdrawal of the rejection of claims 1, 3, 7, 8, 13 and 15 under 35 U.S.C. §103(a) as unpatentable over Lobaccaro et al. is respectfully requested.

Claims 1, 3, 7-8, 13 and 15 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Napolitano et al., J. Med. Chem, Vol. 38, pp. 2774-2779, 1995 (Napolitano et al.). The Examiner essentially contends that since 1) Napolitano et al. teach that the compounds having 11β-substituted estradiol derivatives having R_{11} with less than 5 carbon atoms, which are homologs of the claimed compounds; 2) the derivatives of Napolitano et al. show high affinity for estrogen receptor; 3) the estradiols of Napolitano are known estrogenic compounds and estradiol compounds are well known to be useful in methods for treating estrogen deficiency disorders, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the claimed compounds in a pharmaceutical composition and method for treating estrogen deficiency disorders.

Applicants respectfully traverse the rejection and submit that Napolitano et al. does not make obvious amended claims 1, 8 and 13.

At the outset, the arguments made in the previous response of August 23, 2005 are incorporated by reference herein.

Napolitano et al. is directed to the synthesis of cyanoalkyl, ethynyl, propynyl and iodovinyl 11 β-substituted estradiol derivatives, i.e., derivatives having R_{11} with less than 5 carbon atoms, which are evaluated for binding affinity to the estrogen receptor and for their

potential as imaging agents for estrogen receptor-positive breast tumors. Napolitano is merely concerned with designing high-affinity probes for the estrogen receptor for imaging and is not at all concerned with assessing the specific type of estrogenic activity, i.e., ERα-agonist or ERβ-antagonist, possessed by the described derivatives. Further, Napolitano et al. is devoid of any teaching or specific suggestion that 11β-estradiol derivatives having an R_{11} group of 5 to 6 carbon atoms would possess both ERα-agonist activity and ERβ-antagonist activity. Moreover, Napolitano et al. does not teach or specifically suggest that the described derivatives can be modified to increase the length of the R_{11} group to 5 or 6 carbon atoms. That Napolitano et al. as a whole is merely concerned with increasing the affinity of estradiol derivatives by utilizing various substituents on the R_{11} group for the eventual use of the derivatives as an imaging agent, rather than increasing the chain length of the R_{11} group to 5 or 6 carbon atoms, is evidenced on page 2226, second column, third paragraph (conclusions) wherein it states:

> "In conclusion, four novel series of 11β-substituted estradiol derivatives, differing in the size, polarity, shape, and orientation of the 11β-substituent, were synthesized, and their affinity to the estrogen receptor was determined. Cyanoethyl and cyanopropyl groups at position 11β have a detrimental effect on the binding properties, which is insensitive to the length of the chain. The effect of a 1-alkynyl group at the 11β-position on binding depends on the length of the chain, with the ethynyl group, the binding increased, whereas with the higher homolog 1-propynyl group, it undergoes a marked drop. With iodovinyl estradiols, the binding behavior is strongly dependent on the stereochemistry; the Z isomer binds well, but the E isomer is a poor ligand for the estrogen receptor.
>
> All these data, together with those reported previously, allow us to outline a general strategy for optimizing the binding affinity of estradiol derivatives as candidate receptor-based imaging agents. The possibility for markedly improving the binding affinity of moderately sized estradiol derivatives by placing a substitutent at the 11β-position has definite constraints, since the enhancement of binding appears limited to nonpolar groups whose volume is comparable to or lower than that of an ethyl group. Therefore, as far as the binding affinity is concerned, in designing a receptor-based imaging agent it will probably not be a useful strategy to use an 11β-group to improve binding and to provide a site for the incorporation of the label, if this will make the 11β-group too polar or too large. Rather, it appears to be more fruitful to secure high-binding affinity by using a simple 11β-group (such as a chloromethyl or an ethyl) and then locate the label in a different part of the estradiol molecule."

As can be seen from the above description in Napolitano et al., binding affinity decreased when increasing the length of the 1-alkynyl arm from ethynyl to propynyl. In addition, Napolitano et al. conclude that use of a simple 11β-group (chloromethyl or an ethyl) would be more fruitful in terms of securing high binding affinity. In view of the above description, where is the motivation in Napolitano et al., to increase the chain length on the 11β-position to 5 to 6 carbon atoms to increase binding to ER, let alone to achieve both selective ERα-agonist aand ERβ-antagonist activity to treat estrogen deficient disorders?

In sum, Napolitano et al. does not teach or specifically suggest 11β-estradiol derivatives having an R_{11} linear chain length of 5 to 6 carbon atoms, nor does it teach or specifically suggest that such derivatives would possess both selective ERα-agonist and ERβ-antagonist activity. Further since Napolitano et al. 1) indicate that binding affinity decreases when increasing the length of the 1-alkynyl group from ethynyl to propynyl; 2) conclude that it is more fruitful to have a simple 11β-group (chloromethyl or ethyl); and 3) is completely silent regarding agonist or antagonist activity, one skilled in the art would not be motivated to increase the chain length to 5 to 6 carbon atoms to obtain both agonist and antagonist activity. Moreover, in the lack of a teaching or specific suggestion of utilizing derivatives having an R_{11} linear chain length of 5 to 6 carbon atoms, and lack of motivation to modify the Napolitano et al. derivatives to increase the chain length for the purpose of optimizing affinity binding for use in imaging, let alone to treat estrogen deficiency disorders by inducing ERα agonist activity and ERβ-antagonist activity, one skilled in the art would not have a reasonable expectation of success that 11β-estradiol derivative having an R_{11} linear chain length of from 5 to 6 carbon atoms would possess agonist and antagonist activity and be useful in treating estrogen deficient disorders. Accordingly, Napolitano et al. does not establish a *prima facie* case of obviousness.

As stated above when addressing the rejection of the claims as unpatentable over Lobaccaro et al., an analysis of obviousness of a claimed compound must also include consideration of the results achieved by the claimed compound. Applicants have previously presented a 37 C.F.R. §1.132 Declaration where pharmacologist Antwan Ederveen declared that the differential properties observed between the C4 (an agonist on ERα, see specification, Compound 4 of Table 2) and C5 (an agonist on ERα and antagonist on ERβ) 11β-derivatives is unexpected and does not follow in any way from the teachings of Lobaccaro et al. As amended claims 1, 8 and 13 recite 11β estradiol derivatives having an R_{11} linear chain length of 5 to 6 carbon atoms it is respectfully submitted that the unexpected results are commensurate in scope with the amended claims.

In sum, in view that a *prima facie* case of obviousness has not been established and taking into consideration the unexpected results achieved by the claimed compound, Napolitano et al. does not make obvious claims 1, 3, 7, 8, 13 and 15.

In view of the above, withdrawal of the rejection of claims 1, 3, 7, 8, 13 and 15 as unpatentable over Napolitano et al. is respectfully requested.

A good faith effort has been made to place the present application in condition for allowance. If the Examiner believes a telephone conference would be of value, she is requested to call the undersigned at the number listed below.

Respectfully submitted,

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